Phase II Study of a Comprehensive Treatment Using Perioperative Chemotherapy Combined with Cytoreductive Surgery for Curatively Resected Gastric Cancer Patients with Positive Peritoneal Wash Cytology

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Abstract: Patients with curatively resected gastric cancer patients with positive peritoneal wash cytology are called P0/Cy1 status. The aim of the present study is to verify the survival benefit of the comprehensive treatment for patients with P0/Cy1 status.

Twenty gastric cancer patients were diagnosed as P0/Cy1 by laparoscopy or laparotomy, and were treated with a comprehensive treatment consisting of neoadjuvant intraperitoneal/systemic chemotherapy (NIPS), cytoreductive surgery (CRS) consisting of gastrectomy with lymph node dissection and peritonectomy, intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) and postoperative systemic chemotherapy. At the second look laparotomy, the peritoneal wash cytology became negative in 15 patients. No grade 3, 4, 5 complications were experienced after second look operations for CRS. Median follow-up time is 3.7 years. Eight patients died of recurrence, but the other 21 patients are alive without recurrence. Five-year survival rate was 42%.

The present study demonstrated the efficacy and safety of the comprehensive treatment on the gastric cancer patients in P0/Cy1 status.

Keywords: Peritoneal metastasis, gastric cancer, peritoneal cytology, peritoneal wash cytology.

INTRODUCTION

Peritoneal recurrence is the most common cause of death in advanced gastric cancer patients after curative resection [1, 2]. Peritoneal recurrence is considered to be established from peritoneal free cancer cells (PFCCs) exfoliated from serosal surface invading by primary gastric cancer. By the peritoneal washing cytology, PFCCs are detected in about half of patients with advanced gastric cancer larger than 5 cm in diameter [2]. Because PFCCs have high proliferative activity, they can proliferate on the peritoneal surface or in the subperitoneal initial lymphatic vessels, resulting in the establishment of peritoneal metastasis [3]. Accordingly, the 5-year survival rate of patients with PFCCs is only 2%, even after curative resection [2]. Therefore, positive PFCCs without macroscopic peritoneal metastasis are considered to be peritoneal metastasis. The condition is classified as stage IV disease according to the Japanese Classification of Gastric Cancer [4], and the patients belong to this special group are called P0/Cy1 status. Yamamura Y *et al*. reported that the existence of PFCCs is unlikely to be optimal targets for surgical removal of primary tumor and omental bursa [5].

To eradicate PFCCS, several methods have been reported, but the efficacies of these treatments are still controversial. From the early 1990th, a novel comprehensive treatment consisting of perioperative

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intraperitoneal chemotherapy (PIC) and cytoreductive surgery (CRS) was developed to improve the survival of patients with peritoneal metastasis (PM). In this strategy, macroscopic tumors including primary tumors and metastasis in the regional lymph nodes are completely removed and the residual micrometastases are eradicated with PIC.

The aim of the present study is to verify the survival benefit of the comprehensive treatment for the patients with PFCCs without macroscopic peritoneal metastasis.

PATIENTS AND METHODS

Patients

During 2008 to 2014, 20 curatively resected gastric cancer patients with positive peritoneal wash cytology were treated with a comprehensive treatment consisting of neoadjuvant chemotherapy, gastrectomy with lymph node dissection and peritonectomy, intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) and postoperative systemic chemotherapy.

Eligibility Criteria

The eligibility criteria included: (1) histologically proven primary gastric cancer (2) absence of hematogenous metastasis and remote lymph node metastasis; (3) age 75 years or younger; (4) Eastern Clinical Oncology Group scale of performance status 3 or less; (5) good bone marrow, liver, cardiac, and renal function; (6) absence of other severe medical conditions or synchronous malignancy.

During laparotomy or diagnostic laparoscopy, physiological saline of 200ml was injected into the peritoneal cavity, and peritoneal washings were collected from the cul-de-sac on pelvic cavity. The recovered fluid was centrifuged 5 min at 1500 rpm. The cytospins were obtained with Auto Smear CF-12D (Sakurai Seiki Co., Ltd, Tokyo, Japan). Five slides per one person were prepared and two and one were stained with Papanicolau methods and Alcian blue staining. The other two were fixed with acetone for immunohistochemistry of carcinoembryonic antigen (CEA) and human epithelial antigen, using anti-CEA antibody from Takara Bio. INC, Tokyo, Japan and anti-human epithelial antibody from DAKO, Copenhagen, Denmark.

After diagnosis of P0/Cy1, a peritoneal port system (Hickman Subcutaneous port; BARD, Salt Lake City, UT, USA) was placed in the abdominal cavity, and the tip of the port was introduced on the cul-de-sac of the pelvis, and the abdominal cavity was closed.

Neoadjuvant Intraperitoneal/Systemic Chemotherapy (NIPS)

From 7 days after laparotomy or laparoscopy, patients were treated with oral S1 (Taiho Pharmaceutical Co., Ltd., Tokyo, Japan), twice daily at a dose of 60mg/m^2/day for 14 consecutive days, followed by 7 days rest. Docetaxel and cisplatin were administered intraperitoneally (i.p.) at a dose of 30mg/m^2 on day 1 and day 8. Docetaxel and cisplatin was diluted in 500 ml of normal saline and administered through the implanted peritoneal port system. The treatment course was repeated every 3 weeks for 3 times. This method is named NIPS.

Selection Criteria of Patients for Cytoreductive Surgery (CRS) after NIPS

After three cycles of NIPS, patients who had the following criteria are excluded as the candidates for CRS: 1) evidence of para-aortic lymph node involvement and distant hematogenous metastasis confirmed by computed tomography (CT), or magnetic resonance imaging (MRI), 2) patients with progressive disease after NIPS, or 3) patients with severe co-morbidities or poor general condition.

Cytoreductive Surgery (CRS)

Peritonectomy procedures include partietal peritonectomy, omentectomy with splenectomy, right and left subdiaphragmatic peritonectomy, cholecystectomy, pelvic peritonectomy, lesser omentectomy, and stripping of the omental bursa [6, 7]. The final goal of CRS is to remove primary tumor, the regional lymph nodes and peritoneal metastasis on the peritoneum.

After three weeks of the final course of NIPS, total gastrectomy with D2 lymph node dissection was done in combination with peritonectomy. The peritoneum covering subdiaphragmatic muscle, falciform ligament, coronary ligament, lesser omentum, triangular ligaments, peritoneum covering hepatoduodenal ligament and paracolic gutter were stripped off [6, 7].

In female, the vagina is cut below the uterine cervix after the dissection between pelvic peritoneum and urinary bladder. After the uterine vessels are cut, the rectum is freed from the pelvic structure. Ovaries are removed with uterus and uterine tube. Rectum was cut

1cm below the pelvic peritoneal reflection with a stapler.

Extensve Intraoperative Peritoneal Lavage (EIPL) and Hyperthermic Intraoperative Intraperitoneal Chemotherapy (HIPEC)

After pritonectomy, the peritoneal cavity was filled with 1 L of saline and extensively shaken and washed, Then, the saline was completely aspirated, and this procedure was done 10 times [8]. Then, HIPEC was performed at 43 to 43.5 centigrade for 40 minutes adding 4 liter of saline plus 30 mg/m^2 of docetaxel with cisplatin (50mg/m^2) into the peritoneal cavity.

Oral S1 (60mg/m^2/day) for 14 consecutive days, followed by 7 days rest administration was started from 1 to two months after gastrectomy, and was continued as long as possible.

Institutional review board approval was obtained at October, 20, 2007, as a title of “A comprehensive treatment for the peritoneal dissemination”. All patients signed an informed consent form prior to the comprehensive treatment.

Statistical Analyses

All patients were followed and no patients were lost to follow-up. Outcome data were obtained from medical records and patients’ interview. All statistical analyses were performed using SPSS software statistical computer package version 17 (SPSS Inc., Chicago, USA).

RESULTS

Male and female were 8 and 12, respectively. Average age was 53.2 ± 11.8 years old. Clinicopathologic characteristics are given in Table **1**. Histological type of all patients was poorly differentiated type.

For the neoadjuvant chemotherapy, S1 alone, S1+CDDP, and DCS therapy [9] were administered in each one patient (Table **2**). NIPS (DCS i.p) [10] was done in the other 17 patients. Total gastrectomy was performed in 15 patients, and the other 5 patients underwent distal gastrectomy. All patients were received D2 lymph node dissection.

Bursectomy was done in all patients. Left and right upper quadrant peritonectomy was done in 5 patients, and pelvic peritonectomy was performed in 10 patients. Colectomy was done in one patient.

Table 1: Patients Characteristics

Gender	No.
Male	8
Female	12
Macroscopic type	
Type 3	4
Type 4	15
Type 5	1
Location	
M	5
MLU	15
LN metastasis	
N0	6
N1	7
N2/3	7
Differentiation	
Differentiated	0
Undifferentiated	20

Table 2: Neoadjuvant Chemotherapies and Operation Methods

	No
Neodjuvant chemotherapy	
None	0
Done	
S1 alone	1
S1+CDDP	1
DCS i.v.	1
DCP i.p.	17
Gastrectomy	
Total	15
Distal	5
Lymph node dissection	
D2	20
Hysterectomy	12
Bilateral salpingo-oophorectomy	12
Left upper quadrant peritonectomy	5
Right upper quadrant peritonectomy	5
Peliv peritonectomy	10
Splenectomy	15
Cholecystectomy	17
Mean numbers of resected organ	4.75 (1-9)

At the second look laparotomy, five patients still showed positive peritoneal wash cytology, but the peritoneal wash cytology became negative in the other 15 patients. After NIPS treatment, positive cytology became negative in 13 patients. In contrast, 2 of 3

patients treated with systemic chemotherapy alone showed positive cytology at the second look operation.

No grade 3, 4, 5 complications were experienced after second look operations. Three (15%) patients developed grade 1 and 2 complications and all patients discharged after second look operation.

At October 2nd in 2014, median follow-up time is 3.7 years. Eight patients died of recurrence, but the other 12 patients alive without recurrence. Recurrences were experienced in one patient at esophago-jejunal anastomosis, and seven patients in peritoneal cavity. The survival curve after the second look operation is shown in Figure **1**. Five-year survival rate was 42%.

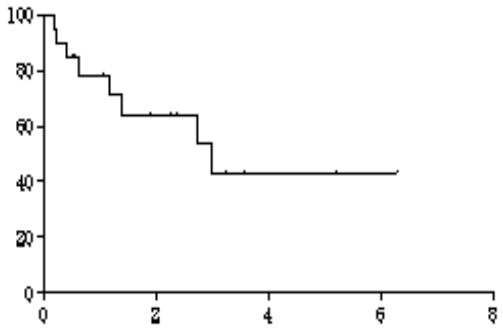

Figure 1: Survival curves of 20 patients with P0/Cy1 status after the comprehensive treatment.

DISCUSSION

Curative resection has been performed in the absence of clinically evident peritoneal disease but without knowledge of cytology status. Bentrem D *et al*. reported that 6.5% of 371 patients underwent R0 resection had positive peritoneal washing cytology, and that the survival of patients with positive cytology was significantly worse than those with negative cytology [12]. In addition, all patients with positive cytology were dead by 3 years. Since the same results about the survival of patients with P0/Cy1 have been reported, positive cases to a peritoneal washing cytology are classified as a distant metastasis on the seventh edition of the UICC TNM staging system [13].

The intraperitoneal cytology status can be diagnosed by laparoscopy before the curative gastric resection is planned [12]. Unfortunately, there is no established consensus to direct treatment for patients in P0/Cy1 status. So far, several treatment regimens have been reported for this particular group of patients.

Shimada *et al*. established intraoperative intraperitoneal chemotherapy (IIPC) with extensive intraperitoneal lavage (EIPL), consisting of washing the intraperitoneal cavity with 1000 ml physiological saline, repeat ten times to achieve the dilution effects. Patients who underwent EIPL with IIPC had a significant improved 5-year survival of 43.8% compared with 4.6% and 0% for those who had IIPC with surgery and surgery alone.

Regarding the results of IIPC with adjuvant chemotherapy on P0/Cy1 patients, three studies were reported [8, 14, 15]. Imano *et al* treated 10 patients by intraperitoneal administration of paclitaxel at a dose of 80 mg/m^2. No viable free cancer cells were observed in the intraabdominal fluid 24 hours after intraperitoneal administration of paclitaxel. Adverse effects as found in 30% (3/10) of their study. Survival of patients treated with IIPC appear to be a trend for improved overall survival as compared with the survival of patients after surgery alone [8, 14].

There were three studies investigating the effects of postoperative S1 monotherapy after curative resection. The 2-year overall survival for patients who were treated with S1 chemotherapy ranged from 47% to 71% [16-18]. Ako *et al* reported that 3-year survival rate of 47 patients treated with S-1 as significantly higher than the 30 patients in control group (no chemotherapy, 71.6% vs 17.1%, HR 0.48, 95% CI 0.32-0.70; P=0.0002) [19].

Three studies evaluated the role of neoadjuvant chemotherapy (NAC) after staging laparoscopy. Badgwell *et al* reported that the 3-year overall survival rate for patients given NAC consisting of external-beam radiation therapy plus systemic chemotherapy as significantly higher than those treated with a palliative approach (12% vs 0%) [20].

Mezhir *et al.* analyzed the 93 patients with P0/Cy1 status and reported that cisplatin-based neoadjuvant chemotherapy had a better median overall survival than those who underwent an immediate gastrectomy [21].

Lorenzen *et al*. examined 61 patients treated with neoadjuvant chemotherapy consisting of cisplatin, folinic acid and fluorouracil [22]. Seven (37%) of 19 patients of P0/Cy1 before NAC reverted from positive to negative after NAC. Patients who became negative cytology after NAC showed an improved survival compared with cytology-positive patients after NAC [22].

Among these studies, recurrence after CRS was more frequently found in the peritoneal cavity (29.4%-55.3%) than in lymph nodes (8.5%-23.5%), liver (2.9%-8.5%), and bone (2.1%-5.7%) [19].

Systemic chemotherapy shows the limits for the treatment of PM. The peritoneal cavity acts as a sanctuary against systemic chemotherapy, because of the existence of a blood-peritoneal barrier [23]. Only a small amount of systemic drugs are capable of penetrating this barrier and passing into the peritoneal cavity. Lorenzen and Mezhir *et al* reported that only 34 (50.7%) of 77 patients reverted from positive to negative cytology after systemic chemotherapy [21, 22]. Furthermore, 10 (24%) of 42 patients with negative cytology before NAC developed positive cytology after NAC [21]. In contrast, Yonemura *et al* reported that the positive cytology results became negative in 69% (47/68) of patients with PM from gastric cancer after NIPS using intraperitoneal administration of CDDP and docetaxel [24].

Accordingly, systemic chemotherapy can not efficiently eradicate peritoneal free cancer cells. In contrast, peritoneal free cancer cells could be efficiently treated by the intraperitoneal chemotherapy, because high loco-regional intensity can be obtained by the intraperitoneal chemotherapy.

The present study demonstrated that positive cytology became negative in 13 (76.4%) patients after NIPS. In contrast, 2 of 3 patients treated with systemic chemotherapy alone showed positive cytology at the second look operation. These results indicate that the intraperitoneal chemotherapy is more effective for the eradication of peritoneal free cancer cells than systemic chemotherapy.

In addition, patients with negative cytology after NIPS survived significantly longer than those with positive cytology after cytoreductive surgery combined with perioperative chemotherapy [24]. Accordingly, intraperitoneal chemotherapy is recommended for P0/Cy1 patients as the neoadjuvant chemotherapy.

The peritoneal recurrence is the most common site of recurrence in patients with P0/Cy1 status after systemic chemotherapy or IIPC combined with gastrectomy and D2 lymphadenectomy. After S1 oral monotherapy, 63 (63.6%) of 99 patients recurred in the peritoneal cavity [16-18]. Kuramoto *et al* reported the peritoneal recurrence was found in 79.3% (23/29) after IIPC using cisplatin. These results indicate that IIPC or S1 chemotherapy alone did not prevent peritoneal recurrence [8].

Therefore, we developed a comprehensive treatment consisting of peritoperative intraperitoneal chemotherapy and cytoreductive surgery using peritonectomy techniques. Before cytoreduction, patients were treated with NIPS. After 3 cycles of NIPS, CRS is planned. Peritoneum covering diaphragm, Morrison's pouch, para-colic gutter and pelvic peritoneum are prone to have peritoneal metastasis [3], and these peritoneal sectors were removed by peritonectomy techniques in combination with gastrectomy and D2 lymph node dissectiopn. Just after CRS, HIPEC using docetaxel and CDDP was done. After the comprehensive treatment, 5-year survival rate was 42%, and only 8 (40%) patients recurred. In addition, no mortality and no grade 3, or 4 morbidities were experienced in the present study.

The present study demonstrated the efficacy and safety of the comprehensive treatment on the gastric cancer patients in P0/Cy1 status. Further studies with large samples size are needed to establish effective treatment for the patients with P0/Cy1 status.

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